Answer 1:

Bibliographic Information

Antitumor activity of fludarabine against human multiple myeloma in vitro and in vivo. Meng, Haitao; Yang, Chunmei; Ni, Wanmao; Ding, Wei; Yang, Xiudi; Qian, Wenbin. Institute of Hematology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, Peop. Rep. China. European Journal of Haematology (2007), 79(6), 486-493. Publisher: Blackwell Publishing Ltd., CODEN: EJHAEC ISSN: 0902-4441. Journal written in English. CAN 148:369397 AN 2008:48519 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Fludarabine, a nucleoside analog, plays a major role in the treatment of B-cell lymphocytic leukemia, hairy cell leukemia, and indolent lymphomas. There is a controversy about antitumor activity of fludarabine in multiple myeloma (MM). The aim of this study was to evaluate the activity of fludarabine against human myeloma cells both in vivo and in vitro. We demonstrated that myeloma cell line RPMI8226 was efficiently inhibited by fludarabine, concomitantly with decreased phosphorylation of Akt, down-regulation of the inhibitor of apoptosis proteins (IAP) family, including XIAP and survivin, and induction of apoptosis related to activation of caspase cascade. Contrary to dexamethasone, the effect of fludarabine on RPMI8226 cells was independent of interleukin-6. Fludarabine also induced cytotoxicity in dexamethasone-sensitive (MM.1S) and -resistant (MM.1R) cells at 48 h with IC50 of 13.48 μg/mL and 33.79 μg/mL, resp. In contrast, U266 cells were resistant to fludarabine. Moreover, RPMI8226 myeloma xenograft model was established using severe combined immunodeficient mice. The tumors treated with fludarabine at 40 mg/kg increased less than 5-fold in 25 d comparing with approx. 10-fold in the control tumors, demonstrating the antitumor activity of fludarabine in vivo. These results suggest that fludarabine may be an important therapeutic option for MM patients who are resistant to dexamethasone.

Answer 2:

Bibliographic Information

Lymphoma Chemovirotherapy: CD20-Targeted and Convertase-Armed Measles Virus Can Synergize with Fludarabine. Ungerechts, Guy; Springfeld, Christoph; Frenzke, Marie E.; Lampe, Johanna; Johnston, Patrick B.; Parker, William B.; Sorscher, Eric J.; Cattaneo, Roberto. Molecular Medicine Program and Virology and Gene Therapy Track, Mayo Clinic College of Medicine, Rochester, MN, USA. Cancer Research (2007), 67(22), 10939-10947. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 148:622 AN 2007:1306230 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Combination chemotherapy regimen incorporating CD20 antibodies are commonly used in the treatment of CD20-pos. non-Hodgkin's lymphoma (NHL). Fludarabine phosphate (F-araAMP), cyclophosphamide, and CD20 antibodies (Rituximab) constitute the FCR regimen for treating selected NHL, including aggressive mantle cell lymphoma (MCL). As an alternative to the CD20 antibody, we generated a CD20-targeted measles virus (MV)-based vector. This vector was also armed with the prodrug convertase purine nucleoside phosphorylase (PNP) that locally converts the active metabolite of F-araAMP to a highly diffusible substance capable of efficiently killing bystander cells. We showed in infected cells that early prodrug administration controls vector spread, whereas late administration enhances cell killing. Control of spread by early prodrug administration was also shown in an animal model: F-araAMP protected genetically modified mice susceptible to MV infection from a potentially lethal intracerebral challenge. Enhanced oncolytic potency after extensive infection was shown in a Burkitt's lymphoma xenograft model (Raji cells): After systemic vector inoculation, prodrug administration enhanced the therapeutic effect synergistically. In a MCL xenograft model (Granta 519 cells), intratumoral (i.t.) vector administration alone had high oncolytic efficacy: All mice experienced complete but temporary tumor regression, and survival was two to four times longer than that of untreated mice. Cells from MCL patients were shown to be sensitive to infection. Thus, synergy of F-araAMP with a PNP-armed and CD20-targeted MV was shown in one lymphoma therapy model after systemic vector inoculation.

Answer 3:

Bibliographic Information

Efficient electrogene therapy for pancreatic adenocarcinoma treatment using the bacterial purine nucleoside phosphorylase suicide gene with fludarabine. Deharvengt, Sophie; Rejiba, Soukaina; Wack, Severine; Aprahamian, Marc; Hajri, Amor. Laboratoire de Biologie des Temeurs et de Therapie Genique, IRCAD-INSERM U701, Strasbourg, Fr. International Journal of Oncology (2007), 30(6), 1397-1406. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 147:250129 AN 2007:704420 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The aim of this study was to demonstrate the potential of electrogene therapy with the bacterial purine nucleoside phosphorylase gene (ePNP), on pancreatic carcinoma (PC) large tumors. The in vivo electroporation (EP) conditions and efficacy were investigated on both s.c. xenografts of human PC cells in immuno-compromised mice and orthotopic intrapancreatic grafts of rat PC cells in syngenic rats. After intratumoral injection of naked plasmid DNA, EP was performed using a two-needle array with 25-ms pulses and either a 300 V/cm field strength for s.c. or a 500 V/cm field strength for orthotopic PC, parameters providing the best electrotransfer as reflected by the measurements of both luciferase activity and ePNP mRNA. As expected, tumors developed sensitivity to prodrug treatment (6-methylpurine deoxyribose or fludarabine phosphate). We obsd. both significant inhibition of tumor growth and extended survival of treated mice. In fact, after prodrug treatment, PC growth in the s.c. model was delayed by 50-70% for ePNP-expressing tumors. In an orthotopic pancreatic tumor model, the animal survival was significantly prolonged after ePNP electrogene transfer followed by fludarabine treatment, with one animal out of 10 being tumor-free 6 mo thereafter. The current study demonstrates for the first time on PC the in vivo feasibility of electrogene transfer and its therapeutic efficiency using the suicide gene/prodrug system, ePNP/fludarabine. These findings suggest that electrogene therapy strategy must be considered for pancreatic cancer treatment, particularly at advanced stages of the disease.

Answer 4:

Bibliographic Information

Protein kinase C inhibitor enzastaurin induces in vitro and in vivo antitumor activity in Waldenstrom macroglobulinemia. Moreau, Anne-Sophie; Jia, Xiaoying; Ngo, Hai T.; Leleu, Xavier; O'Sullivan, Garrett; Alsayed, Yazan; Leontovich, Alexey; Podar, Klaus; Kutok, Jeffrey; Daley, John; Lazo-Kallanian, Suzan; Hatjiharissi, Evdoxia; Raab, Marc S.; Xu, Lian; Treon, Steven P.; Hideshima, Teru; Anderson, Kenneth C.; Ghobrial, Irene M. Dana-Farber Cancer Institute, Boston, MA, USA. Blood (2007), 109(11), 4964-4972. Publisher: American Society of Hematology, CODEN: BLOOAW ISSN: 0006-4971. Journal written in English. CAN 147:1179 AN 2007:627402 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Waldenstrom macroglobulinemia (WM) is an incurable lymphoplasmacytic lymphoma with limited options of therapy. Protein kinase Cβ (PKCβ) regulates cell survival and growth in many B-cell malignancies. In this study, we demonstrate up-regulation of PKCβ protein in WM using protein array techniques and immunohistochem. Enzastaurin, a PKCβ inhibitor, blocked PKCβ activity and induced a significant decrease of proliferation at 48 h in WM cell lines (IC50, 2.5-10 μM). Similar effects were demonstrated in primary CD19+ WM cells, without cytotoxicity on peripheral blood mononuclear cells. In addn., enzastaurin overcame tumor cell growth induced by coculture of WM cells with bone marrow stromal cells. Enzastaurin induced dose-dependent apoptosis at 48 h mediated via induction of caspase-3, caspase-8, caspase-9, and PARP cleavage. Enzastaurin inhibited Akt phosphorylation and Akt kinase activity, as well as downstream p-MARCKS and ribosomal p-S6. Furthermore, enzastaurin demonstrated additive cytotoxicity in combination with bortezomib, and synergistic cytotoxicity in combination with fludarabine. Finally, in an in vivo xenograft model of human WM, significant inhibition of tumor growth was obsd. in the enzastaurin-treated mice (p = .028). Our studies therefore show that enzastaurin has significant antitumor activity in WM both in vitro and in vivo, providing the framework for clin. trials to improve patient outcome in WM.

Answer 5:

Bibliographic Information

Antitumor activity of a monoclonal antibody against CD47 in xenograft models of human leukemia. Uno, Shinsuke; Kinoshita, Yasuko; Azuma, Yumiko; Tsunenari, Toshiaki; Yoshimura, Yasushi; Iida, Shinichiro; Kikuchi, Yasufumi; Yamada-Okabe, Hisafumi; Fukushima, Naoshi. Fuji-Gotemba Research Labs, Chugai Pharmaceutical Co., Ltd., Shizuoka, Japan. Oncology Reports (2007), 17(5), 1189-1194. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 147:342026 AN 2007:548516 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The ligation of CD47 induces the apoptosis of leukemic cells in a caspase-independent manner. We generated a monoclonal antibody against CD47 (mAb-MABL) that possibly induced apoptosis from the ligation of CD47 in CCRF-CEM and JOK-1 cells in vitro. To confirm whether the ligation of CD47 caused cell death in vivo, we examd. the antitumor activity of F(ab')2 of mAb-MABL in two xenograft models: The acute lymphoblastic leukemia (CCRF-CEM) and the B-cell chronic lymphocytic leukemia (JOK-1) cell line. Furthermore, in order to clarify the apoptotic activity selective for the tumor cells, we examd. F(ab')2 of mAb-MABL apoptotic effects on CD34+ hematopoietic progenitor/stem and human endothelial cells. Male SCID mice were i.v. injected with CCRF-CEM (5 × 106 cells/mouse) or JOK-1 cells (5 × 106 cells/mouse) and i.p. with JOK-1 cells (2 × 107 cells/mice). After the implantation of the cells, the mice were i.v. administered the vehicle or the F(ab')2 fragment of mAb-MABL at several doses and the length of survival was measured. F(ab')2 of mAb-MABL markedly prolonged the survival of mice transplanted with CCRF-CEM and JOK-1. Significantly, 40% of the mice i.p. injected with JOK-1 cells became tumor-free when administered F(ab')2 of mAb-MABL, whereas even a high dose of fludarabine only slightly prolonged the median survival time. On the contrary, F(ab')2 of mAb-MABL showed no apoptotic effect on CD34+ hematopoietic progenitor/stem or human endothelial cells. Thus, monoclonal antibodies that cause cell death from the ligation of CD47 could be novel therapeutic agents for incurable leukemia after further optimization such as humanization or making single chain diabodies.

Answer 6:

Bibliographic Information

Anti-tumor efficacy of Cloretazine (VNP40101M) alone and in combination with fludarabine in murine tumor and human xenograft tumor models. Zheng, Li-mou; Li, Zujin; Liu, Lanzhen; Song, Bai Louis; King, Ivan. Vion Pharmaceutical, Inc., New Haven, CT, USA. Cancer Chemotherapy and Pharmacology (2007), 60(1), 45-51. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 147:180783 AN 2007:447320 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Cloretazine (VNP40101M), a new sulfonylhydrazine alkylating agent, has demonstrated broad-spectrum anti-tumor activity in preclin. studies. In this study, Cloretazine was evaluated both as a monotherapy and in combination with fludarabine in murine tumor and human tumor xenograft models. Cloretazine significantly inhibited the growth of s.c. implanted tumors, including B16F10 murine melanoma in C57BL/6 mice, and H460 human lung carcinoma and WiDr human colon carcinoma in athymic nude CD1 mice. The inhibition of tumor growth by Cloretazine was dose dependent, increasing from 42.2 to 87% as the dose escalated from 100 to 150 mg/kg. Cloretazine showed equiv. efficacy but lower toxicity compared to cyclophosphamide in these models. The combination therapy, consisting of a single dose of 10 mg/kg Cloretazine plus five doses of 70 mg/kg fludarabine, given every other day i.p., significantly increased the long-term survival of BDF1 mice bearing the L1210 murine leukemia. On Day 65 post-tumor implantation, the combination therapy yielded a 90% survival rate compared to 40% for Cloretazine alone and 0% for fludarabine alone.

Answer 7:

Bibliographic Information

Preclinical evaluation of a prostate-targeted gene-directed enzyme prodrug therapy delivered by ovine atadenovirus.
Wang, X. Y.; Martiniello-Wilks, R.; Shaw, J. M.; Ho, T.; Coulston, N.; Cooke-Yarborough, C.; Molloy, P. L.; Cameron, F.; Moghaddam, M.; Lockett, T. J.; Webster, L. K.; Smith, I. K.; Both, G. W.; Russell, P. J. Oncology Research Centre, Prince of Wales Hospital Clinical School of Medicine, The University of New South Wales, Randwick, Australia. Gene Therapy (2004), 11(21), 1559-1567. Publisher: Nature Publishing Group, CODEN: GETHEC ISSN: 0969-7128. Journal written in English. CAN 141:343077 AN 2004:834796 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Gene-directed enzyme prodrug therapy (GDEPT) based on the Escherichia coli enzyme, purine nucleoside phosphorylase (PNP), provides a novel strategy for treating slowly growing tumors like prostate cancer (CaP). PNP converts systemically administered prodrug, fludarabine phosphate, to a toxic metabolite, 2-fluoroadenine, that kills PNP-expressing and nearby cells by inhibiting DNA, RNA and protein synthesis. Reporter gene expression directed by a hybrid prostate-directed promoter and enhancer, PSMEPb, was assayed after plasmid transfection or viral transduction of prostate and non-CaP cell lines. Androgen-sensitive (AS) LNCaP-LN3 and androgen-independent (AI) PC3 human CaP xenografts in nude mice were injected intratumorally with an ovine atadenovirus vector, OAdV623, that carries the PNP gene under PSMEPb, formulated with cationic lipid for enhanced infectivity. Fludarabine phosphate was then given i.p. for 5 days at 75 mg/m2/day. PNP expression was evaluated by enzymic conversion of its substrate using reverse phase HPLC. OAdV623 showed excellent in vitro transcriptional specificity for CaP cells. In vivo, expression of PNP persisted for >6 days after OAdV623 injection and a single treatment provided 100% increase in tumor doubling time and >50% inhibition of tumor growth for both LNCaP-LN3 and PC3 lines, with increased tumor necrosis and apoptosis and decreased tumor cell proliferation. OAdV623 significantly suppressed the growth of AS and AI human CaP xenografts in mice.

Answer 8:

Bibliographic Information

Gene therapy for prostate cancer delivered by ovine adenovirus and mediated by purine nucleoside phosphorylase and fludarabine in mouse models. Voeks, D.; Martiniello-Wilks, R.; Madden, V.; Smith, K.; Bennetts, E.; Both, G. W.; Russell, P. J. Oncology Research Centre, Prince of Wales Hospital, Sydney, Australia. Gene Therapy (2002), 9(12), 759-768. Publisher: Nature Publishing Group, CODEN: GETHEC ISSN: 0969-7128. Journal written in English. CAN 137:362643 AN 2002:431746 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A gene-directed enzyme prodrug therapy (GDEPT) based on purine nucleoside phosphorylase (PNP), that converts the prodrug, fludarabine to 2-fluoroadenine, has been described, but studies are limited compared with other GDEPTs. The authors investigated the in vitro and in vivo efficacies of PNP-GDEPT for treating androgen-independent (AI) prostate cancer. The PNP gene controlled by Rous sarcoma virus (RSV) constitutive promoter was delivered using a recombinant ovine adenovirus vector (OAdV220) that uses a different receptor from human adenovirus type 5. In vitro, OAdV220 provided increased transgene expression over a comparable human Ad5 vector in infected AI, murine RM1 prostate cancer cells. Subsequent in vivo testing was therefore confined to OAdV220. Transduction of RM1 cells with OAdV220 before implantation in immunocompetent mice dramatically inhibited s.c. tumor growth when fludarabine phosphate was administered systemically and increased mouse survival in a dose-dependent manner. In tumor-bearing C57BL/6 mice, a single intratumoral injection of OAdV220 produced detectable PNP activity for at least 6 days and with prodrug, retarded the growth of aggressive RM1 s.c. tumors by 35% at day 14. There was a consistent trend to redn. of pre-established intraprostatic RM1 tumors. A similar regimen induced significant therapeutic efficacy in human PC3 xenografts. Thus, ovine adenovirus-mediated GDEPT using the PNP system was effective in vivo against AI prostate cancers, the aggressive murine RM1, and the human PC3 lines. Methods that improve viral dissemination and stimulate the immune system in vivo may further improve efficacy.

Answer 9:

Bibliographic Information

Potentiation of 2-chlorodeoxyadenosine activity by bryostatin 1 in the resistant chronic lymphocytic leukemia cell line (WSU-CLL). Association with increased ratios of dCK/5'-NT and Bax/Bcl-2. Mohammad, Ramzi M.; Beck, Frances W. J.; Katato, Khalil; Hamdy, Nayera; Wall, Nathan; Al-Katib, Ayad. Department Medicine, Division Hematology Oncology, Karmanos Cancer Institute, School Medicine, Wayne State University, Detroit, MI, USA. Biological Chemistry (1998), 379(10), 1253-1261. Publisher: Walter de Gruyter & Co., CODEN: BICHF3 ISSN: 1431-6730. Journal written in English. CAN 129:270219 AN 1998:685786 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The activities of 2-chlorodeoxyadenosine (2-CdA) metabolizing enzymes, deoxycytidine kinase (dCK) and cytosolic 5'-nucleotidase (5'-NT) were measured in bryostatin 1 treated chronic lymphocytic leukemia (CLL) cells using an EBV-neg. WSU-CLL cell line. This cell line was established from a patient with CLL resistant to fludarabine. The results revealed an increase in dCK activity in bryostatin 1 treated cells at 48 and 72 h compared with the control. 5'-NT activity decreased at 48 h. The ratio of dCK to 5'-NT activity was increased in bryostatin 1 treated WSU-CLL cells after 48 h. WSU-CLL cells treated with bryostatin 1 exhibited an increase in the % of apoptotic and dead cells from control levels of 16% to 40%. This % was further increased to 67% following the addn. of 11.2 μM 2-CdA to WSU-CLL cells pretreated with bryostatin 1. Results from Western blot indicate that WSU-CLL cells express high levels of Bcl-2, Bcl-xL, and c-myc, and a low level of Bax. P53 in untreated WSU-CLL cells is undetectable. WSU-CLL cells treated with bryostatin 1 showed an increase in the ratio of Bax:Bcl-2. To demonstrate that the bryostatin 1 mediated enhancement of 2-CdA efficacy was not restricted to in vitro cell culture, the authors have studied the tumor growth delay of WSU-CLL xenografts treated with placebo, bryostatin 1, 2-CdA, and bryostatin 1 followed by 2-CdA. SCID mice given bryostatin 1 at 75 μg × kg-1 × d-1 for 5 days followed by 30 mg × kg-1 × d-1 2-CdA for 5 days in 2 cycles, had improved tumor growth delay. The authors conclude that bryostatin 1 is not only capable of inducing apoptosis by itself, but also sensitizes de novo resistant WSU-CLL cells to the chemotherapeutic effects of 2-CdA. The bryostatin 1 induced increased ratio of dCK/5'-NT activity and an increased ratio of Bax/Bcl-2 are at least 2 mechanisms through which this natural compd. is able to potentiate the antitumor activity of 2-CdA in otherwise resistant CLL cells.

Answer 10:

Bibliographic Information

Sequential treatment of human chronic lymphocytic leukemia with bryostatin 1 followed by 2-chlorodeoxyadenosine: preclinical studies. Mohammad, Ramzi M.; Katato, Khalil; Almatchy, Victor P.; Wall, Nathan; Liu, Kan-Zhi; Schultz, Christian P.; Mantsch, Henry H.; Varterasian, Mary; Al-Katib, Ayad M. Division of Hematology and Oncology, Karmanos Cancer Institute, Department of Medicine, Wayne State University School of Medicine, Detroit, MI, USA. Clinical Cancer Research (1998), 4(2), 445-453. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 128:239082 AN 1998:130543 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The authors have previously reported that bryostatin 1 (Bryo 1) induces differentiation of chronic lymphocytic leukemia (CLL) in vitro to a hairy cell (HC) stage. This study tests the hypothesis that Bryo 1-differentiated CLL cells are more susceptible to 2-chlorodeoxyadenosine (2-CdA) than parent CLL cells. A recently established EBV-neg. CLL line (WSU-CLL) from a patient resistant to chemotherapy including fludarabine was used to test this hypothesis. Both Bryo 1 (10-1000 nM) and 2-CdA (5.6-22.4 μM) exhibited a dose-dependent growth inhibitory effect on the WSU-CLL cell line. In vitro, the sequential exposure to Bryo 1 (100 nM for 72 h) followed by 2-CdA (11.2 μM) resulted in significantly higher rates of growth inhibition than either agent alone. Changes in immunophenotype, enzymes, lipids, proteins, and the DNA of WSU-CLL cells were studied before and after Bryo 1 treatment. Bryo 1 induced a pos. tartrate-resistant acid phosphatase reaction and two important markers, CD11c and CD25, after 72 h of culture, confirming the differentiation of CLL to HC. The Fourier transformation IR spectroscopic anal. showed that the amt. of membrane lipids significantly increased in Bryo 1-treated cells compared to controls after 24 h, whereas the protein content, as well as the DNA content, decreased. This finding supports the change of CLL to HC. To evaluate the in vivo efficacy of Bryo 1 and 2-CdA, the authors used a xenograft model of CLL in WSU-CLL-bearing mice with severe combined immune deficiency. S.c. tumors were developed by injection of 107 WSU-CLL cells, and fragments were then transplanted into a new batch of severe combined immunodeficient mice. Bryo 1 and 2-CdA at the max. tolerated doses (75 μg/kg i.p. and 30 mg/kg s.c., resp.) were administered to the mice at different combinations and schedules.

The survival in days, the tumor growth inhibition ratio, the tumor growth delay, and the log10 kill of the mice treated with Bryo 1 followed by 2-CdA were significantly better than the control and other groups. The authors conclude that the sequential treatment with Bryo 1 followed by 2-CdA resulted in higher antitumor activity and improved animal survival.

Answer 11:

Bibliographic Information

In vivo gene therapy of cancer with E. coli purine nucleoside phosphorylase. Parker, William B.; King, Scott A.; Allan, Paula W.; Bennett, L. Lee, Jr.; Secrist, John A., III; Montgomery, John A.; Gilbert, Karen S.; Waud, William R.; Wells, Alan H.; Gillespie, G. Yancey; Sorscher, Eric J. Southern Research Institute, Birmingham, AL, USA. Human Gene Therapy (1997), 8(14), 1637-1644. Publisher: Liebert, CODEN: HGTHE3 ISSN: 1043-0342. Journal written in English. CAN 127:326065 AN 1997:653799 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We have developed a new strategy for the gene therapy of cancer based on the activation of purine nucleoside analogs by transduced E. coli purine nucleoside phosphorylase (PNP, E.C. 2.4.2.1). The approach is designed to generate antimetabolites intracellularly that would be too toxic for systemic administration. To det. whether this strategy could be used to kill tumor cells without host toxicity, nude mice bearing human malignant D54MG glioma tumors expressing E. coli PNP (D54-PNP) were treated with either 6-methylpurine-2'-deoxyriboside (MeP-dR) or arabinofuranosyl-2-fluoroadenine monophosphate (F-araAMP, fludarabine, a precursor of F-araA). Both prodrugs exhibited significant antitumor activity against established D54-PNP tumors at doses that produced no discernible systemic toxicity. Significantly, MeP-dR was curative against this slow growing solid tumor after only 3 doses. The antitumor effects showed a dose dependence on both the amt. of prodrug given and the level of E. coli PNP expression within tumor xenografts. These results indicated that a strategy using E. coli PNP to create highly toxic, membrane permeant compds. that kill both replicating and nonreplicating cells is feasible in vivo, further supporting development of this cancer gene therapy approach.

Answer 12:

Bibliographic Information

Mediation of apoptosis by and antitumor activity of lumiliximab in chronic lymphocytic leukemia cells and CD23+ lymphoma cell lines. Pathan Nuzhat I; Chu Peter; Hariharan Kandasamy; Cheney Carolyn; Molina Arturo; Byrd John Department of Oncology Cell Signaling, Biogen Idec, San Diego, CA 92122, USA. nuzhat.pathan@biogenidec.com Blood (2008), 111(3), 1594-602. Journal code: 7603509. ISSN:0006-4971. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 18032710 AN 2008060549 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Lumiliximab is a chimeric macaque-human monoclonal antibody to CD23, a protein expressed on virtually all chronic lymphocytic leukemia (CLL) cells. We examined the ability of lumiliximab to mediate apoptosis, antibody-dependent cellular cytotoxicity, and complement-dependent cytotoxicity against primary CLL cells and CD23-expressing B-cell lines. Our data suggest that lumiliximab kills CLL cells and CD23-expressing B cells predominantly by apoptosis, which occurs through the intrinsic pathway. Lumiliximab-induced apoptosis was accompanied by the down-regulation of antiapoptotic proteins Bcl-2, Bcl-X(L), and XIAP, activation of Bax, and release of cytochrome c from the mitochondria. We also found that the addition of lumiliximab to rituximab or fludarabine results in synergistic cytotoxicity of primary CLL cells and CD23-expressing B-cell lines. We investigated the in vivo activity of lumiliximab in a human disseminated CD23(+) B-cell lymphoma SCID mouse model and found greater antitumor activity with it than with control antibody. We also found that paralysis-free survival was greater with lumiliximab plus rituximab or fludarabine than with any of those agents alone. These results suggest that lumiliximab may be an effective treatment alone or in combination with rituximab or chemotherapy agents in CLL or other CD23-overexpressing B-cell malignancies.

Answer 13:

Bibliographic Information

Delivery of replication-competent retrovirus expressing Escherichia coli purine nucleoside phosphorylase increases the metabolism of the prodrug, fludarabine phosphate and suppresses the growth of bladder tumor xenografts. Kikuchi E; Menendez S; Ozu C; Ohori M; Cordon-Cardo C; Logg C R; Kasahara N; Bochner B H Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA Cancer gene therapy (2007), 14(3), 279-86. Journal code: 9432230. ISSN:0929-1903. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 17218950 AN 2007098845 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

We have developed unique replication-competent retroviral (RCR) vectors based on murine leukemia virus that provide improved efficiency of viral delivery, allow for long-term transgene expression and demonstrate an intrinsic selectivity for transduction of rapidly dividing tumor cells. The purpose of this study was to evaluate the in vivo transduction efficiency and the therapeutic efficacy of the RCR vector mediated delivery of Escherichia coli purine nucleoside phosphorylase (PNP) in combination with fludarabine phosphate for bladder cancer. We constructed vectors containing green fluorescent protein (GFP) gene (ACE)-GFP) or PNP gene (ACE-PNP). KU-19-19 bladder tumors exhibited 28.3+/-16.1, 46.6+/-5.8 and 93.7+/-7.8% of GFP expression on 14, 18 and 26 days after intratumoral injection of ACE-GFP, respectively. GFP expression could not be observed in normal tissues surrounding the injected tumors. No detectable polymerase chain reaction products of GFP gene could be observed in any distant organs. Intratumoral injection of ACE-PNP, followed by systemically administered fludarabine phosphate, significantly inhibited the growth of pre-established KU-19-19 tumors. Our results indicate that RCR vectors are a potentially efficient gene delivery method and that the RCR vector mediated PNP gene transfer and fludarabine phosphate treatment might be a novel and potentially therapeutic modality for bladder cancer.

Answer 14:

Bibliographic Information

Excellent in vivo bystander activity of fludarabine phosphate against human glioma xenografts that express the escherichia coli purine nucleoside phosphorylase gene. Hong Jeong S; Waud William R; Levasseur Dana N; Townes Tim M; Wen Hui; McPherson Sylvia A; Moore Bryan A; Bebok Zsuzsa; Allan Paula W; Secrist John A 3rd; Parker William B; Sorscher Eric J Department of Cell Biology, University of Alabama at Birmingham, Birmingham, Alabama 35294-0005, USA Cancer research (2004), 64(18), 6610-5. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 15374975 AN 2004464625 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Escherichia coli purine nucleoside phosphorylase (PNP) expressed in tumors converts relatively nontoxic prodrugs into membrane-permeant cytotoxic compounds with high bystander activity. In the present study, we examined tumor regressions resulting from treatment with E. coli PNP and fludarabine phosphate (F-araAMP), a clinically approved compound used in the treatment of hematologic malignancies. We tested bystander killing with an adenoviral construct expressing E. coli PNP and then more formally examined thresholds for the bystander effect, using both MuLv and lentiviral vectoring. Because of the importance of understanding the mechanism of bystander action and the limits to this anticancer strategy, we also evaluated in vivo variables related to the expression of E. coli PNP (level of E. coli PNP activity in tumors, ectopic expression in liver, percentage of tumor cells transduced in situ, and accumulation of active metabolites in tumors). Our results indicate that F-araAMP confers excellent in vivo dose-dependent inhibition of bystander tumor cells, including strong responses in subcutaneous human glioma xenografts when 95 to 97.5% of the tumor mass is composed of bystander cells. These findings define levels of E. coli PNP expression necessary for

antitumor activity with F-araAMP and demonstrate new potential for a clinically approved compound in solid tumor therapy.

Answer 15:

Bibliographic Information

A human B-cell CLL model established by transplantation of JOK-1 cells into SCID mice and an anti-leukemia efficacy of fludarabine phosphate. Bai L; Kon K; Tatsumi M; Ito H; Hayashi S; Brautigam M Preclinical Development Department, R&D, Nihon Schering K.K., Yodogawa-ku, Osaka 532-0004, Japan Oncology reports (2000), 7(1), 33-8. Journal code: 9422756. ISSN:1021-335X. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 10601587 AN 2000070582 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The present study was carried out to establish a human chronic lymphocytic leukemia (CLL) mouse model by transplantation of a JOK-1 human CLL cell line into SCID (severe combined immunodeficient) mice and to examine anti-leukemic effects of fludarabine phosphate, a prodrug of 9-beta-D-arabinofuranosyl-2-fluoroadenine (2F-ara-A). In vitro cytotoxic screening pattern of 2F-ara-A differed from those of other anticancer agents. Intraperitoneal inoculation with JOK-1 cells in SCID mice allowed the cells to infiltrate into a variety of organs including the liver and thymus, and resulted in the death of the mice with a median survival time of 29.5 days, associated with hepatomegaly, splenomegaly and enlarged lymph nodes. The ascitic cells expressing the human B-lymphocytic cell surface antigen CD19 actually grew after a latent period of 15 days. In this model, twice daily administration of fludarabine phosphate at a dose of 135 mg/kg for 5 days prolonged the survival time of the mice for considerably longer period than once-a-day treatment. Fludarabine phosphate in the doubled course of twice daily increased life span of 32.9%, which was in a similar range to that of doxorubicin. Thus, intraperitoneal inoculation of the human JOK-1 CLL cells into SCID mice seems to serve as an animal model potentially for human leukemia, suggesting that transplantation and subsequent infiltration processes of human CLL cells is useful measures to explore mechanistic aspects for drug-induced modulation of the tumor progression.

Answer 16:

Bibliographic Information

Treatment of a de novo fludarabine resistant-CLL xenograft model with bryostatin 1 followed by fludarabine. Mohammad R M; Limvarapuss C; Hamdy N; Dutcher B S; Beck F W; Wall N R; Al-Katib A M Division of Hematology and Oncology, Wayne State University School of Medicine, Lande Medical Research Building, Room 317, Detroit, MI 48201, USA International journal of oncology (1999), 14(5), 945-50. Journal code: 9306042. ISSN:1019-6439. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 10200346 AN 1999218376 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

WSU-CLL is a de novo fludarabine resistant cell line established from a patient with advanced chronic lymphocytic leukemia (CLL) refractory to chemotherapy including fludarabine (Flud). Our previous studies indicate that bryostatin 1 (Bryo 1) induces differentiation of WSU-CLL and increases the ratio of dCK/5'-NT activity and Bax/Bcl-2. This study tests the hypothesis that Bryo 1-differentiated cells are more susceptible to Flud than the parent WSU-CLL cells. Flud, given sequentially after Bryo 1, in vitro and in vivo animal studies resulted in significantly higher rates of growth inhibition and improved animal survival. Flud at 100 to 600 nM exhibited a dose-dependent growth inhibitory effect on the WSU-CLL cell line. The sequential exposure to Bryo 1 (10 nM for 72 h) followed by Flud (100 nM) resulted in significantly

higher rates of growth inhibition than either the reverse addition of these two agents or each agent alone, but was not significantly different than the concurrent addition of Bryo 1 + Flud. Using 7-amino-actinomycin D staining and flow cytometry, apoptosis was seen in 40.8% of cells treated with Bryo 1 (10 nM, 72 h) followed by Flud, compared with Flud (100 nM, 72 h) followed by Bryo 1 (18.1%). To demonstrate that Bryo 1 enhancement of Flud efficacy was not restricted to in vitro culture, we used the WSU-CLL xenograft model in mice with severe combined immune deficiency (SCID). Bryo 1 + Flud at the maximum tolerated doses (75 microg/kg i.p. and 200 mg/kg i.v., respectively) were administered to mice in different combinations. The survival in days, the tumor growth inhibition ratio (T/C), the tumor growth delay (T-C) in days, log10 kill, as well as mean tumor weight (mtw) of mice treated with Bryo 1 followed by Flud, were significantly better than control and other groups. T/C%, T-C, log10 kill and mtw were as follows: Bryo 1 (36.8%, 10 days, 0.8, 375 mg); Flud (100%, 0. 0 day, 0.0, 1130 mg); Bryo 1 + Flud (14.3%, 12 days, 0.95, 288 mg);
Bryo 1 followed by Flud (4.6%, 17 days, 1.35, 35 mg); Flud followed by Bryo (40.3%, 10 days, 0.80, 175 mg). We conclude that: i) Bryo 1 sensitizes WSU-CLL cells to Flud and enhances apoptosis; ii) the sequential treatment with Bryo 1 followed by Flud resulted in higher anti-tumor activity compared with either agent alone, in combination, or the reverse addition of these agents and iii) these results are comparable to those of Bryo 1 followed by 2-CdA suggesting common pathway(s) of interaction between Bryo 1 and purine analogues.

Answer 17:

Bibliographic Information

Antitumor activity of 2-chloro-9-(2-deoxy-2-fluoro-beta-D-arabinofuranosyl) adenine, a novel deoxyadenosine analog, against human colon tumor xenografts by oral administration. Takahashi T; Kanazawa J; Akinaga S; Tamaoki T; Okabe M Cancer Chemotherapy, Pharmaceutical Research Institute, Kyowa Hakko Kogyo Co. Ltd., Japan Cancer chemotherapy and pharmacology (1999), 43(3), 233-40. Journal code: 7806519. ISSN:0344-5704. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 9923554 AN 1999120429 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

2-Chloro-9-(2-deoxy-2-fluoro-beta-D-arabinofuranosyl) adenine (Cl-F-araA) is a novel deoxyadenosine analog, which inhibits DNA synthesis by inhibiting DNA polymerase alpha and ribonucleotide reductase. Cl-F-araA shows potent antiproliferative activity against several leukemic cell lines including those of human origin and is also effective against murine solid tumors, in particular being curative against colon tumors. PURPOSE: We therefore decided to investigate whether Cl-F-araA is effective against human colon tumors, in particular by oral administration, since it has improved stability compared with other deoxyadenosine analogs. METHODS: Antiproliferative activity in vitro was determined from cell counts. Subcutaneously inoculated xenograft models and a liver micrometastases model were used for assessment of antitumor activity in vivo. RESULTS: Cl-F-araA showed potent antiproliferative activity against four human colon tumor cell lines (HCT116, HT-29, DLD-1, WiDr), with a 50% growth-inhibitory concentration (IC50) of 0.26 microM with a 72-h exposure. This activity was greater than those of fludarabine desphosphate and cladribine, other deoxyadenosine analogs, which showed IC50 values of 19 microM and 0.35 microM, respectively. Cl-F-araA showed potent antitumor activity against four human colon tumor xenograft models (HT-29, WiDr, Co-3, COLO-320DM) in a 5-day daily administration schedule, which was shown to be the most effective of three administration regimens tested (single, twice-weekly, 5-day daily). In particular, oral administration showed significantly superior activity, with a regressive or cytostatic growth curve, compared with intravenous administration. In addition, Cl-F-araA was effective at only one-sixteenth of the maximum dose tested in a 10-day daily administration schedule. Therapeutic efficiency seemed to increase in proportion to the frequency of administration.

Cl-F-araA also decreased liver micrometastases created by intrasplenic injection of human colon tumor cells, leading to complete suppression at the maximum dose tested. CONCLUSIONS: These results suggest that Cl-F-araA might be clinically effective against human colon cancers using a daily oral administration schedule.

Answer 18:

Bibliographic Information

Chemotherapy of subcutaneous and intracranial human medulloblastoma xenografts in athymic nude mice.
Friedman H S; Schold S C Jr; Bigner D D Cancer research (1986), 46(1), 224-8. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 2415246 AN 86053222 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The continuous human medulloblastoma cell line TE-671 was grown as s.c. and intracranial xenografts in athymic nude mice. Tumor-bearing animals were treated with chemotherapeutic agents at the 10% lethal dose; s.c. xenografts were sensitive to melphalan, 1-(2-chloroethyl)-3-(2,6-dioxo-1-piperidyl)-1-nitrosourea, and 5-azacytidine. No consistent response could be demonstrated to 9-beta-D-arabinofuranosyl-2-fluoroadenine 5'-monophosphate, and no response to methylglyoxal bis(guanyl hydrazone), N-trifluoroacetyl adriamycin-14-valerate, or to 1-beta-D-arabinofuranosylcytosine was observed. Melphalan produced a significant (P = less than or equal to 0.007) increase in the median survival of mice bearing intracranial xenografts, whereas no response was seen to 1-(2-chloroethyl)-3-(2,6-dioxo-1-piperidyl)-1-nitrosourea or 5-azacytidine. This model will allow analysis of the chemotherapeutic profile of human medulloblastoma, and provides a means to differentiate cellular sensitivity and resistance from drug access to the intracranial site.